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Relationship of Femorodistal Bypass Patency to Clinical Outcome

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Objective: *to investigate the relationship between bypass patency, limb survival and clinical symptoms after femorodistal bypass procedures.*
Design: *multicentre, prospectively planned 12-month postoperative follow-up.*
Patients and methods: *five hundred and seventeen patients undergoing femorodistal bypass surgery for severe ischaemia. Clinical symptoms, bypass patency were recorded at regular intervals up to 12 months postoperatively.*
Results: *complete follow-up data was obtained on 498 patients (96%). Fifty-six (17%) of the 341 patients with patent bypasses had either rest pain or ulcers or had undergone major amputation at 12 months. Of the 167 patients with an occluded bypass, 22 patients (13%) had improved clinical symptoms and a total of 59 patients (35%) had avoided major amputation at 12 months. The clinical outcome for patients classified preoperatively as Fontaine stage IV was significantly worse than for those in stage III preoperatively despite similar bypass patency rates.*
Conclusions: *there is a fair correlation between technical and clinical outcome after femorodistal bypass surgery at 12 months, but there are significant numbers of patients with occluded bypasses who have a good clinical outcome and of patients with patent bypasses who have a poor clinical outcome. The reporting of symptoms in addition to bypass patency would aid the interpretation of surgical results.*

Key Words: Femorodistal bypass; Patency; Amputation; Clinical outcome.

Introduction

Results of studies to evaluate distal arterial reconstructions are usually presented as bypass patency and limb survival. Information on further interventions may give patency subdivided into primary, assisted primary and secondary patency. This method is much concerned with the technical outcome of the procedures. The clinical success of the procedure is usually described only in terms of limb salvage and it is rare that long-term follow-up of clinical symptoms is reported. This is surprising as it is these very symptoms which were the reason for the surgical intervention. The interpretation of the effectiveness of a surgical procedure would be aided by information on either the patient's symptoms or quality of life postoperatively.

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Both bypass patency and limb salvage rates are conventionally estimated using life-table methods.[1] This method effectively excludes patients who have died or are otherwise lost to follow-up and estimates the patency rate for each interval based on the patients who have survived to the beginning of this interval and whose fate is known. The assumption made, that the outcome in patients who were assessed in a given interval is likely to represent the outcome in all those entered into a study, has recently been challenged and the need for more complete information advocated.[2] To the information on patency and limb salvage is sometimes added mortality, but there is usually little information on clinical outcome.

It has previously been reported that bypass occlusion does not inevitably lead to amputation[3] and that some patients with chronic critical ischaemia may improve without an operation.[4] A recent prospective clinical trial of adjuvant intravenous iloprost in femorodistal bypass surgery confirmed that there were some differences between the number of patients retaining

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their limbs at 12 months and the number with relief symptoms.[5] Data from this study were investigated retrospectively in order to find out the extent to which bypass patency and limb salvage results are sufficient to judge the clinical outcome of these vascular surgical procedures.

Methods

Patients were studied prospectively during a trial of adjuvant pharmacotherapy in femorodistal bypass procedures.[5] Twenty-one centres included a total of 517 patients. The protocol was approved by the appropriate Ethics Committees for each of the participating centres.

The patients studied were those undergoing bypass surgery for severe ischaemia with the proximal anastomosis above the knee and the distal anastomosis below the knee and principally to the tibioperoneal trunk, the anterior tibial, posterior tibial or peroneal artery. On entry into the study and prior to surgery all patients were classified as having peripheral arterial occlusive disease (PAOD) in stage III or stage IV according to the Fontaine classification, with ischaemic rest pain of at least 14 days' duration or trophic lesions of arterial origin or both.

Presence or absence of ulcers, gangrene, rest pain and intermittent claudication, and the use of analgesics were all documented before surgery and at 14 days, 3 months and 12 months after surgery. During follow-up, the Fontaine stages were recorded as follows: Fontaine stage I was defined as no symptoms of ischaemia in the relevant leg, stage II as intermittent claudication, stage III as ischaemic rest pain or the use of analgesia to control rest pain and stage IV as the presence of ischaemic ulcers or gangrene with or without rest pain. Bypass patency was recorded at the same intervals as clinical symptoms and was confirmed by angiography or duplex ultrasound if necessary. Further surgical interventions including amputation were recorded whenever they occurred during follow-up.

Assessments of clinical symptoms and bypass patency for each patient were both based on the limb operated on entry into the study. Only one reconstructed limb per patient was included. For the purpose of comparisons with clinical outcome, bypass patency included successfully reopened grafts (secondary patency). Bypass patency figures reflect the number of patients actually alive with patency of the original bypass at the time of assessment. Clinical success of the procedures was defined as a classification of PAOD in Fontaine stage I or II. The time course of the resolution of symptoms was investigated and compared with the technical success of the bypass procedures. Patients' symptoms were compared in those with patent and occluded bypasses and the patients were divided according to preoperative Fontaine stage.

Data were analysed according to the intent-to-treat (ITT) principle. All patients entered into the study are accounted for and percentages refer to the 517 patients entered unless otherwise stated. Comparison of patency rates in different sub-groups was performed using log-rank tests to compare pairs of curves. Comparisons of continuous data in different groups of patients was performed using the Mann–Whitney Rank Sum test and the Mantel–Haenszel Chi-squared test was used for comparison of categorical data at a single time-point.

Results

Patients and surgical procedures

The 517 patients entered into the study consisted of 317 male and 199 women (one patient was not classified) with a mean age of 71 (range 30–90). Diabetes mellitus was recorded in 36% of patients and 35% admitted to being current smokers. PAOD preoperatively was classified as stage III in 34% and stage IV in 65%. Four patients were entered with only intermittent claudication. In total 499 patients (97%) had rest pain indicating that almost all of the patients in stage IV had rest pain in addition to trophic lesions. Four hundred and six patients (79%) were receiving analgesia. Ulcers were present in 256 patients (50%) and gangrene in 221 (43%) with 140 patients (27%) having both. Mean ankle pressure ($\pm$S.D.) on entry was 56 mmHg ($\pm$41) and the mean ankle-brachial pressure index 0.65 ($\pm$0.32). Previous myocardial and cerebral infarctions were recorded in 23% and 11% of patients, respectively.

The majority of distal anastomoses were made to anterior and posterior tibial arteries and to the peroneal artery. The distribution of the distal anastomoses between these three vessels and between the different levels in the calf was fairly even (Table 1). Vein grafts were used in 424 procedures (82%) and prosthetic or prosthetic-vein composite grafts in 92 (18%). Graft material in one procedure was unclassified. Additional bypass grafts in the same limb were performed in 24 patients during the 12 month follow-up after occlusion of the initial bypass.

Table 1. Sites of distal anastomoses.

Artery	Level of distal anastomosis (no. of patients (%))			
	Upper	Mid	Lower	Totals
Below knee popliteal	9 (1.8)	0 (0.0)	0 (0.0)	9 (1.8)
Tibioperoneal trunk	40 (7.7)	2 (0.4)	2 (0.4)	44 (8.5)
Anterior tibial	56 (10.8)	53 (10.3)	70 (13.5)	179 (34.6)
Posterior tibial	22 (4.3)	57 (11.0)	65 (12.6)	144 (27.9)
Peroneal	46 (8.9)	55 (10.6)	38 (7.4)	139 (26.9)
Dorsalis pedis	0 (0.0)	0 (0.0)	2 (0.4)	2 (0.4)
All vessels	173 (33.5)	167 (32.3)	177 (34.2)	517 (100.0)

Bypass patency results

Information on bypass patency up to 12 months after surgery was obtained in 508 patients (98%). The percentage of patients in the study alive with an intact limb and patent bypass at 12 months irrespective of graft material were 45% with primary patency and 52% with secondary patency. Primary graft patencies at 12 months for vein and prosthetic grafts were 45% and 40%, respectively. Secondary patency was 53% in vein grafts and 46% in prosthetic grafts.

Bypass patency in patients who were classified as Fontaine stage III and stage IV preoperatively did not differ ($p=0.91$). Similar results were found for bypass patency with and without rest pain ($p=0.71$) and for patency with and without gangrene preoperatively ($p=0.36$).

Clinical outcome

Information on clinical outcomes up to 12 months after surgery was available on 507 patients (98%). Over the 12 months' follow-up 103 patients (20%) underwent a major amputation of the operated leg. A total of 93 patients (18%) died during follow-up, eight of whom had undergone major amputation and 85 of whom had not. Comparison of limb salvage rates in stage III and stage IV patients showed a trend towards a higher amputation rate in stage IV patients ($p=0.063$).

The number of patients with rest pain was greatly reduced post-operatively and most of those patients with continuing rest pain suffered only intermittently (Fig. 1) and were not using opiate analgesics (Fig. 2). The incidence of trophic lesions was reduced more slowly postoperatively than the incidence of rest pain and the use of analgesia, but after 12 months only 45 patients (13% of those with lesions preoperatively) still had trophic lesions (Fig. 3). Very few had gangrene.

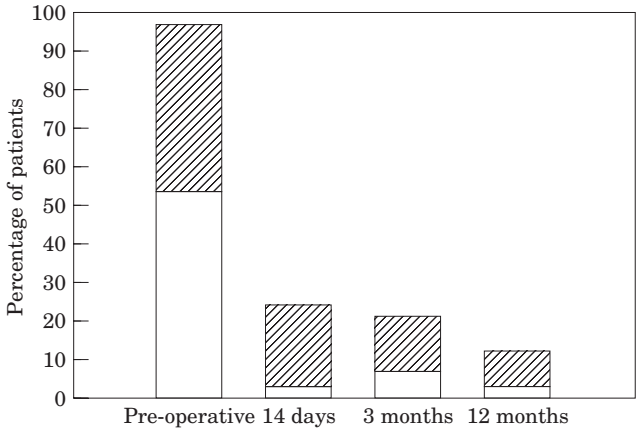

Fig. 1. Incidence of rest pain over 12 months. (□) Continuous; (▨) intermittent.

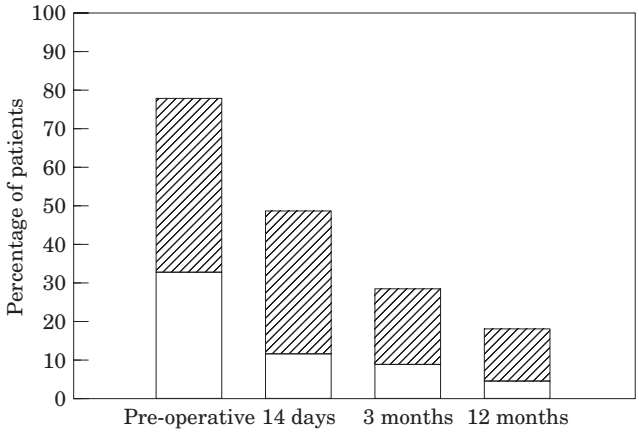

Fig. 2. Use of analgesics over 12 months. (□) Opiate; (▨) non-opiate.

Relationship of bypass patency to clinical outcome

Information on both bypass patency and clinical outcome up to 12 months after surgery was available on 498 patients (96%). The proportion of patients with patent grafts at 12 months, 52%, did not differ greatly

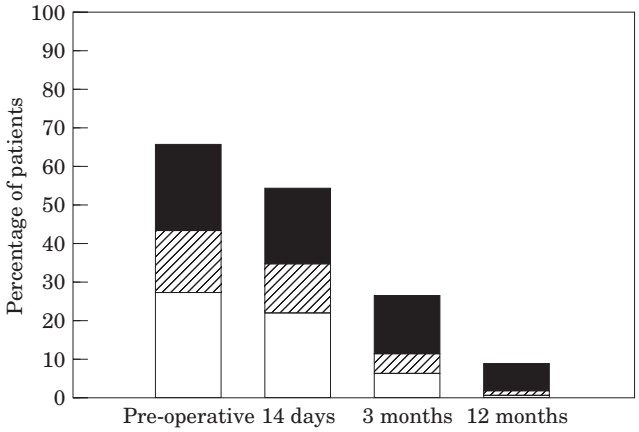

Fig. 3. Presence of trophic lesions over 12 months. (□) Ulcers plus gangrene; (▨) gangrene; (■) ulcers.

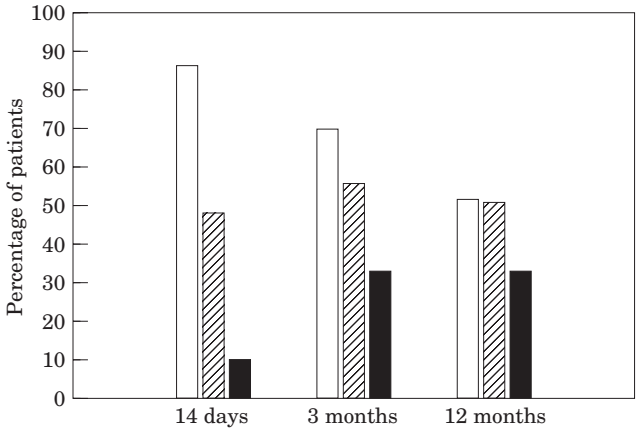

Fig. 4. Comparison of technical and clinical success in evaluable patients. (□) Graft patency; (▨) relief of rest pain; (■) healing of ulcers.

from 46% reporting only mild or no ischaemic symptoms (Fontaine stage I or II). However, this was the case only after 12 months. At 14 days and 3 months there were fewer patients with improved clinical symptoms than with a patent graft (Fig. 4). This was particularly true for those patients with trophic lesions, in whom resolution of symptoms took longer.

Amongst patients alive at 12 months without a major amputation in the relevant leg, there was a large measure of agreement between technical and clinical success. Eighty-four per cent of these patients with patent bypasses were in Fontaine stage I or II and 90% of all patients in stage I or II had a patent graft (Table 2), although over half of the patients alive and in Fontaine stage III or IV had patent bypasses.

The majority of patients whose bypasses did not permanently occlude were in stage I/II at 12 months and only 5% of these patients underwent major amputations. In contrast, 55% of patients with an occluded bypass went on to have a major amputation and most of those alive without an amputation had rest pain or ischaemic ulcers. In total, 128 patients with occluded bypasses were alive at 12 months. In those patients whose bypasses had occluded, duration of patency was compared in those with a favourable and an unfavourable outcome. The duration of patency in those undergoing a major amputation within the 12 months' follow-up period (median 26 days) was significantly shorter than in those patients retaining their limb (median 68 days), $p = 0.019$. The duration of patency in patients without substantial clinical improvement (stage III/IV or having undergone major amputation) at 12 months (median 42 days) was not significantly shorter than the duration of patency in those patient with clinical improvement (stage I/II) at 12 months (median 79 days), although there was a similar trend, $p = 0.066$. These differences did not indicate a threshold duration of bypass patency beyond which amputation was unlikely or clinical improvement was assured. Patients at risk of later occlusion could also not be identified by continuing symptoms of ischaemia. The proportion of patients with continuing rest pain at discharge was identical amongst those patients who later suffered an occlusion and amongst those whose bypasses remained patent.

The clinical outcome was influenced by the preoperative Fontaine stage (Table 3). In the case of a patent bypass, patients who were in stage III before surgery were less likely to have died ($p = 0.004$) and, if alive without a major amputation, were more likely to be in stage I or II at 12 months ($p = 0.008$) than those who were in stage IV preoperatively. If the bypass had occluded and not been reopened at 12 months, there was no significant association of preoperative Fontaine stage with mortality and amputation rates, but preoperative stage III patients, who were alive without a major amputation, were more likely to have improved to stage I or II ($p = 0.04$).

Patients with a preoperative stage III had overall a 60% likelihood of being alive without a major amputation and in stage I or II at 12 months compared to a 38% likelihood for patients with trophic lesions preoperatively. The overall difference in mortality was also significant, 10% in stage III and 23% in stage IV ($p = 0.0004$), but the difference in incidence of major amputations, 18% in stage III and 22% in stage IV was not significant ($p = 0.22$).

Table 2. Clinical outcome of all patients at 12 months.

Patency of bypass at 12 months or at time of death or amputation	Patent ($n=341$)	Occluded ($n=167$)
Clinical outcome	No. of patients (%)	No. of patients (%)
Stage I/II	215 (63%)	22 (13%)
Stage III/IV	40 (12%)	37 (22%)
Amputated*	16 (5%)	89 (53%)
Dead†	67 (20%)	26 (16%)
Not recorded	6 (2%)	4 (2%)

*Includes patients who were dead at 12 months, but previously amputated.
†Includes patients who had previously been amputated.

Table 3. Relationship of clinical outcome at 12 months to preoperative Fontaine stage.

Patency at 12 months or at amputation or death	Patent ($n=340$)		Occluded ($n=167$)	
Preoperative stage:	Stage III ($n=116$)	Stage IV ($n=224$)	Stage III ($n=58$)	Stage IV ($n=109$)
Clinical outcome	No. patients (%)	No. patients (%)	No. patients (%)	No. patients (%)
Stage I/II	94 (81%)	121 (54%)	14 (24%)	8 (7%)
Stage III/IV	8 (7%)	32 (14%)	12 (21%)	25 (23%)
Amputated*	2 (2%)	14 (6%)	28 (48%)	61 (56%)
Dead†	10 (9%)	57 (25%)	8 (14%)	18 (17%)
Not recorded	2 (2%)	4 (2%)	2 (4%)	2 (2%)

* Includes patients who were dead at 12 months, but previously amputated.
† Includes patients who had previously been amputated.

Twenty-two patients who had suffered a bypass occlusion were, nonetheless, in stage I or II at 12 months. Prior to femorodistal bypass 14 (64%) of these patients were in stage III, five (23%) had gangrene and two (9%) had diabetes mellitus. Ten (45%) of them (five stage III preoperatively and five stage IV) had received a second bypass in the same leg.

Fifty-six patients with a patent bypass at 12 months were still in Fontaine stage III or IV or had undergone major amputation without bypass occlusion due to a lack of improvement in symptoms. The majority of these patients (82%) were in stage IV preoperatively and 36 patients (64%) had gangrene prior to surgery. Twenty-seven (48%) of them had diabetes mellitus.

Discussion

From reports in the vascular surgery literature, it is often difficult to assess the impact of distal arterial reconstructions on the patients. It has been proposed that the clinical outcome should be included in studies dealing with lower extremity ischaemia[6] and exceptionally studies report clinical outcomes in detail.[7] Bypass patency and limb salvage results are often the only data on which the success of distal arterial reconstructions are judged. This study, performed in 21 vascular centres from six countries, shows that less than half of the patients undergoing distal bypass surgery are both alive without amputation and having no symptoms or only mild symptoms of ischaemia after 12 months. It was also found that surgical success frequently does not equate to the relief of symptoms.

The large increase in ankle pressure recorded after a successful distal reconstruction in a severely ischaemic limb[8] leads to the expectation that a rapid improvement in the clinical symptoms would follow. In this study 517 patients were followed up for 12 months after femorodistal bypass procedures for chronic ischaemia. Complete follow-up of both bypass patency and clinical outcome were obtained in 96% of cases. This is an unusually high rate of follow-up and provided the opportunity to investigate the extent to which patency and limb salvage are a sufficient guide to the clinical results.

The patency rates appear low compared to many other published series, but it should be borne in mind that the figures reported here are the absolute numbers of patients with a patent graft, not a probability of graft patency, and do not exclude patients who die or undergo major amputation. This is in contrast to most reports. The results after 12 months' follow-up support the conclusion that many of the patients with a patent bypass have an improvement in their symptoms, al-

though less than two-thirds could be classified in Fontaine stage I or II. The improvement seemed to be relatively slight in the first 14 days after surgery. It could be expected that ischaemic ulcers and gangrene, and wounds from associated minor amputation procedures, might require a longer healing period. That rest pain requires a longer period to resolve completely is more unexpected. A possible explanation is the difficulty which both the surgeon and the patient may have experienced in distinguishing between rest pain and pain associated with trophic lesions. Almost two-thirds of the patients with rest pain also had trophic lesions on entry into the study. Pain from the surgical wound could have played a role after 14 days, though hardly after 3 months.

In this study clinical outcome was described using the Fontaine classification with pain, analgesic use and trophic lesions subdivided only into a small number of well-defined categories which could be easily applied in a multicentre study. A possible criticism is that the definition of Fontaine stages III and IV was broad with all patients suffering from any pain at rest or receiving any analgesics for the control of ischaemic pain being classed as stage III. It was shown even after only 14 days that few patients were still suffering from continuous pain or requiring opiate analgesics. Similarly, patients with any trophic lesion were classed as stage IV and partial healing of lesions was not recorded. Other classifications of clinical status have been suggested,[6,9] but these are more complicated and were avoided since they may be subject to differing interpretations in different hospitals. Bypass patency rates in this study include secondary patency, as this is more likely to influence the clinical outcome than purely primary patency.

The results in patients whose bypasses were occluded and not reopened showed that this did not always lead to major amputation. Almost 40% of these patients were alive without a major amputation after 1 year and 14% could still be described as being improved. It has been stated that the purpose of a bypass operation in patients with critical ischaemia is to avoid amputation and that any outcome which includes an intact limb may qualify as a success.[10] By this criterion, many patients with a bypass occlusion still had a successful clinical outcome. A clinical improvement despite an occluded bypass does not necessarily imply that these operations were not indicated. Critical ischaemia may be viewed as an acute exacerbation of a chronic condition and a period of improved blood supply may be sufficient to allow the healing of a trophic lesion, for example, which could explain the longer-term success despite the occlusion of the graft. This explanation is supported by the difference in this study between the duration of patency in patients with favourable and unfavourable clinical outcomes after bypass occlusion.

The overall rates of major amputation and death are in agreement with those obtained from a large vascular registry[10] and an earlier prospective study.[11] Major amputation in patients with a patent graft occurred in only 5%, which compares favourably with the 8% reported in another study in a similar population.[12] Interestingly, the rate of major amputation was 11 times higher in patients with an occluded graft, but the more frequent requirement for a second major operation within a year in those with occlusions did not lead to a greater mortality. The mortality was in fact slightly, though not statistically, higher in those patients with patent bypasses.

It is documented that trophic lesions in PAOD are associated with a higher mortality.[13,14] In contrast to a previous report,[12] the major amputation rate in this study was not significantly higher in patients with lesions. However, the differences in clinical outcome were striking, despite similar patency rates in patients with stage III and IV preoperatively. Very few stage IV patients can expect to have no symptoms or only claudication at 12 months if their bypass occludes, although a third of those surviving may avoid major amputation. Even if a bypass remains patent, only just over half of the stage IV patients will have a good clinical outcome while the figure for stage III patients was 90%. In patients who received a second bypass it is difficult to judge the contribution of the initial bypass to the long-term clinical result. However, it is notable that five of the eight patients who were in stage IV preoperative and stage I or II at 12 months despite an occluded initial bypass had received a second bypass. In these cases the second procedures most probably account for some of the clinical improvement. This serves to stress still further the difference in progress between patients in stage III preoperatively and those in stage IV.

This study demonstrates that there is a reasonable correlation between patency of distal arterial reconstructions and clinical outcome in the long-term. However, with 17% of patients with patent bypass grafts either amputated or still in Fontaine stage III or IV after 12 months, and 35% limb survival in patients with occluded grafts, any evaluation of new surgical techniques or adjuvant therapy should include an assessment of clinical outcome in addition to patency. An alternative approach would be the assessment of quality of life after bypass surgery. Appropriate scales are being developed[15] and these could also prove to

be a useful tool in investigating the clinical outcome of distal bypass surgery.

References

1 Underwood CJ, Faragher EB, Charlesworth D. The uses and abuses of life-table methods in vascular surgery. *Br J Surg* 1984; **71**: 495–498.
2 Jensen LP, Nielsen OM, Schroeder TV. The importance of complete follow-up for results after femoroinfrapopliteal vascular surgery. *Eur J Vasc Endovasc Surg* 1996; **12**: 282–286.
3 Veith FJ, Gupta SK, Ascer E *et al*. Six-year prospective multicentre randomized comparison of autologous saphenous vein and expanded polytetrafluoroethylene grafts in infrainguinal arterial reconstructions. *J Vasc Surg* 1986; **3**: 104–114.
4 Sørensen S, Lorentzen JE, Schroeder TV. Prognosis for limb-loss in patients with chronic critical ischemia considered technically inoperable. *Vasc Surg* 1992; **26**: 283–289.
5 Iloprost Bypass International Study Group. Effect of perioperative iloprost on patency of femorocrural bypass grafts. *Eur J Vasc Endovasc Surg* 1996; **12**: 363–371.
6 Rutherford RB, Baker JD, Ernst C *et al*. Recommended standards for reports dealing with lower extremity ischaemia: revised version. *J Vasc Surg* 1997; **26**: 517–538.
7 Ray SA, Minty I, Buckenham TM, Belli A-M, Taylor RS, Dormandy JA. Clinical outcome and restenosis following percutaneous transluminal angioplasty for ischaemic rest pain or ulceration. *Br J Surg* 1995; **82**: 1217–1221.
8 Harling H, Lorentzen JE, Nielson OM, Buchardt Hansen HJ. Femorodistal bypass – a worthwhile procedure? *Eur J Vasc Surg* 1987; **1**: 133–135.
9 Belch JJF. Evaluating treatment of critical limb ischaemia. *Critical Ischaemia* 1992; **2**: 5–12.
10 Troëng T, Bergqvist D, Janson L. Incidence and causes of adverse outcomes of operation for chronic ischaemia of the leg. *Eur J Surg* 1994; **160**: 17–25.
11 Wolfe JHN. Defining the outcome of critical ischaemia: a 1-year prospective study. *Br J Surg* 1986; **73**: 321.
12 Dietzek AM, Gupta SK, Kram HB, Wengerter KR, Veith FJ. Limb-loss with patent infrainguinal bypasses. *Eur J Vasc Surg* 1990; **4**: 413–417.
13 Rafferty TD, Avellone JC, Farell CJ *et al*. A metropolitan experience with infrainguinal revascularization: operative risks and late results in north-eastern Ohio. *J Vasc Surg* 1987; **6**: 365–371.
14 DeWeese JA, Rob CG. Autogenous venous grafts 10 years later. *Surgery* 1977; **82**: 775–784.
15 Beattie DK, Golledge J, Greenhalgh RM, Davies AH. Quality of life assessment in vascular disease: towards a consensus. *Eur J Vasc Endovasc Surg* 1997; **13**: 9–13.

Appendix

The Iloprost Bypass International Study Group

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